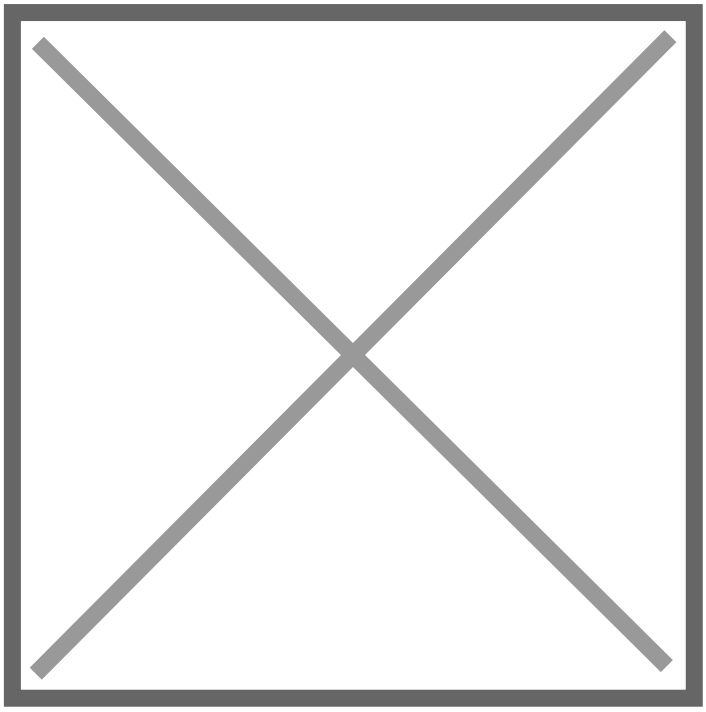
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IBM helps fight against Dengue

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The World Community Grid is the world's largest public computing grid to tackle scientific research projects that benefit humanity

Finding drugs to treat diseases such as dengue hemorrhagic fever, hepatitis C, West Nile encephalitis, and yellow fever has been a perennial challenge for scientists. Till date there have been no effective drugs to treat these diseases. Consequently, the supportive care necessary to treat these infections and minimize mortality severely strains the already burdened health facilities throughout the world.

With this in mind, IBM, along with representatives of the world's leading science, education and philanthropic organizations, launched World Community Grid in November 2004. It is a multimillion dollar investment by IBM to create the world's largest public computing grid to manage scientific research projects that benefit humanity. IBM donated the hardware, software, technical services and expertise to build the infrastructure for World Community Grid. IBM also provides free hosting, maintenance and support.

The World Community Grid

Harnessing power

Millions of personal computers sit idly on desks and in homes worldwide. By 2008, analysts estimate PCs to reach 1 billion. The World Community Grid is a global humanitarian effort that hopes to harness the collective power of millions of individual PCs and business computers so that complex computations can be completed in a fraction of the time typically required.

Projects

A total of seven projects have been run on the community grid. Five projects are now completed: They are Help Defeat Cancer project, Genome Comparison project, Help Cure Muscular Dystrophy, and the first phase of the Human Proteome Folding project. The two active projects now on the Grid are: Human Proteome Folding project in the second phase and Fight AIDS@ Home.

Collaborations

IBM has enlisted an advisory board consisting of senior members from IBM, key foundations, academia (with the University of Texas Medical branch and the University of Chicago) and public agencies to review projects submitted via the RFP. The goal is to assure that World Community Grid resources are focused on research that has the greatest impact and support work that might otherwise be bypassed in favor of more commercial projects.

Discovering Dengue Drugs - Together

The University of Texas Medical Branch and the University of Chicago have joined hands with World Community Grid researchers to combat some of the most widespread viral diseases under the project "Discovering Dengue Drugs-Together." This project will discover promising both broad-spectrum and specific antiviral drugs that stop the replication of viruses within the Flaviviridae family responsible for dengue hemorrhagic fever, hepatitis C, West Nile encephalitis, and yellow fever.

The approach

These viruses can be combated from causing diseases by developing drugs that inhibit the viral NS3 protease. The NS3 protease is an enzyme critical for virus replication, and its amino acid sequence and atomic structure are very similar among the different diseaseÃ¢â?¬â??causing flaviviruses. Since the atomic structure of the NS3 protease is known, advanced structureÃ¢â?¬â??based computational drug discovery methods can be used to identify small molecule protease inhibitors.

Dr Stan Watowich and his research team at the University of Texas Medical Branch (Galveston, Texas, USA) have made significant progress in this direction, having discovered compounds that inhibit dengue and West Nile virus proteases and prevent virus replication in cell culture. However, additional drug candidates need to be discovered to improve the likelihood of converting drug leads into approved drugs for treating flavivirus infections.

How it works

Using the megacomputing power of World Community Grid, researchers at the University of Texas Medical Branch will complete extensive drug discovery calculations that will accurately predict binding free energies (a measure of how strongly molecules interact) between small drug-like molecules and different flavivirus NS3 proteases.

In Phase 1 of this project, AutoDock will fit over six million small molecules to each of the flavivirus NS3 proteases, so optimal binding orientations can be identified. AutoDock, developed by Dr Arthur Olson of The Scripps Research Institute (San Diego, California, USA) can predict how small molecules might fit into a binding "pocket" on a protein of known atomic structure. These docking calculations will provide orientations for each small molecule-protease complex and a preliminary metric to discriminate between possible protease inhibitors and non-binding molecules.

In Phase 2 of this project, potential protease inhibitors predicted by Autodock will be organized into a concise database for detailed analysis with CHARMM, a molecular dynamics program developed by Prof. Martin Karplus and his colleagues at Harvard University (Cambridge, Massachusetts, USA). Accurate CHARMM-based mean field binding free energy calculations

will be applied to all potential protease inhibitors.

The post-processing of the initial fitting results with binding free energy calculations will significantly reduce false-positive rates, thus speeding discovery of potent protease inhibitors.

Novel compounds predicted to be high-affinity inhibitors of flavivirus proteases will be tested in laboratory assays for antiviral activity. Running these complex drug discovery calculations on World Community Grid will dramatically reduce the time required to complete this computationally intensive project.

Dengue virus (DENV) infects 50 million (WHO) to 100 million (NIH) people annually. Forty percent of the world's population, predominately in the tropics and sub-tropics, is at risk for contracting dengue virus. Dengue fever is a severe, fluÃ¢â?¬â??like illness typically accompanied by very high fever and severe joint pain. Dengue hemorrhagic fever is a frequent complication of dengue virus infection, characterized by intense fever, internal bleeding, and circulatory failure; death occurs in 5 percent of patients. In India specifically, Dengue fever has affected more than 46,000 children and adults between 2001 and 2006 of which almost 700 were fatal. Delhi and Rajasthan alone accounted for 43 percent of the cases

Shalini Gupta